

### **REMARKS**

The present application is directed to compositions comprising novel polycationic carbohydrates. In particular, the present application is directed to novel polycationic compounds wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan, or a pharmaceutically acceptable salt or derivative thereof, or a mixture thereof. In addition, methods for the use of the above polycationic carbohydrates as an immunostimulant are disclosed. Claims 1-39 are pending. Claims 7-10 and 24-35 are withdrawn as being directed to a non-elected species. Claims 1-6, 11-23, 26 and 29 are currently amended. New Claims 36-39 are added. Support for the following remarks is found throughout the specification, and no new matter is introduced. In light of the following remarks, favorable consideration of the present application is respectfully requested.

#### **Claim rejections under 35 U.S.C. §112, first paragraph**

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claims 1-6 and 11-23 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner stated the specification only sets forth immunostimulants such as chitin derivatives, chitosan or chemically modified forms of chitosan. Applicants respectfully traverse the Examiner's rejection.

Applicants concur that immunostimulants such as chitin derivatives, chitosan or chemically modified forms of chitosan are disclosed in the instant application. Furthermore, applicants assert that the present invention discloses chitosan or a mixture of chitosan with other positively charged molecules. Support for the proposed mixtures can be found in the instant application on at least, page 15, lines 21-24. Accordingly, Applicants respectfully submit that the written description is commensurate in scope with the claims. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph and request its withdrawal.

**Claim rejections under 35 U.S.C. §112, second paragraph**

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claims 1-6 and 11-23 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner stated it is unclear from Claim 1 whether the polycationic carbohydrate is 1) a water-soluble alkylated chitosan 2) a cationic polypeptide, 3) a cationic polyamino acid and 4) quaternary ammonium compound OR if the cationic polypeptide, cationic polyamino acid, quaternary ammonium compound or mixtures thereof are particular examples of the polycationic carbohydrate or pharmaceutically acceptable derivatives thereof.

Applicants respectfully submit that the amendments to the claims overcome the rejection. The pending claims recite a polycationic carbohydrate comprising a water-soluble alkylated chitosan, or a pharmaceutically acceptable salt or derivative thereof, or a mixture thereof, for use as an immunostimulant. Accordingly, Applicants submit the polycationic carbohydrate is now definite and request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

The Examiner stated the claims are unclear in regard to a pharmaceutically acceptable salt. Applicants respectfully submit that one of ordinary skill in the art would be capable of defining a pharmaceutically acceptable salt. Indeed, it is well known in the pharmaceutical sciences that salt derivatives can be used in place of, or in addition to, the parent compound. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

The Examiner stated the use of the term “such as” in Claim 2 renders the claims indefinite. Applicants have amended the claim to delete the above term and assert Claim 2 is now definite. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

The Examiner stated Claims 2-6 and 11-23 are required to recite the appropriate claim language. Applicants respectfully submit the Claims are amended herein to recite “the pharmaceutical composition” or “the polycationic composition” as suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

Finally, the Examiner stated the term “biologically active agent” in Claims 4, 6, 16 and 23 is indefinite. Applicants respectfully traverse the rejection. Applicants respectfully submit that one of ordinary skill in the art would be capable of defining a biologically active agent. Furthermore, Applicants direct the Examiner to page 11, lines 25-36 and page 5, line 1-page 6, line 13 of the instant application, wherein the Applicants disclose several examples of biologically active agents. Accordingly, Applicants submit the Claims are definite and request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

**Claim rejections under 35 U.S.C. §102(b)**

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claims 1-2, 4-6, 11-12, 16 and 18-19 under 35 U.S.C. §102(b), as being anticipated by Illum (WO 97/20576) (hereinafter the “Illum patent”).

Applicants respectfully traverse the rejection. The pending claims are directed to a pharmaceutical composition comprising a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan, or a pharmaceutically acceptable salt or derivative thereof, or a mixture thereof, for use as an immunostimulant. Applicants respectfully submit that Illum fail to teach or suggest a polycationic carbohydrate comprising an alkylated chitosan.

Furthermore, Applicants respectfully submit Illum fail to teach or suggest chitosan has an adjuvant effect in a vaccine composition other than an intra-nasal vaccine composition. The “chitosan” of Illum is made by deacetylating chitin and is preferably water soluble (see page 5 lines 21-24). The example provided is commercially available chitosan, chitosan glutamate. As acknowledged by Illum, chitosan glutamate is only water soluble in a narrow band of relatively acidic pH. This disadvantage is discussed on page 7, lines 1-4 of Illum. Clearly, in order for the composition to remain soluble the composition cannot be universally applicable to all pharmaceutical sites. Moreover, the chitosan composition of Illum is not suitable to all mucosal sites, for example the gastrointestinal tract because of the various pH portions along the tract. In contrast, the compositions of the instant application have been found to have an immunostimulatory effect at a broad range of biological sites, for example, see page 8, lines 22-

32. As such, the compositions of the instant application have a far wider range of pharmaceutical application than those disclosed by Illum. Accordingly, Applicants submit they have overcome the Examiner's rejection under 35 U.S.C. §102(b) and request its withdrawal.

**Claim rejections under 35 U.S.C. §103(a)**

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claims 13-15, 17 and 20-22 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Eyles et al., (hereinafter "Eyles").

Applicants respectfully traverse. As explained above, Illum fail to teach or suggest a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition. In addition, Claims 13-15, 17 and 20-22 depend directly or indirectly from the composition of Claim 1. As discussed above Applicants respectfully submit the compositions of the instant application are novel and non-obvious over the teachings of Illum. Furthermore, the deficiencies of Illum are not satisfied by Eyles for at least the following reasons.

Eyles fail to teach a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition, or use thereof. Eyles disclose a study of intra-nasal immunization with microencapsulated F1 and V antigens. The results of which show it is possible to protect against inhalation of *Y. pestis* by intra-nasal administration of a combined subunit vaccine. Microencapsulation of the subunits and the non-toxic subunit of cholera toxin (CTB) led to elevated immunological responses by intra-nasal route. Supporting the documented adjuvant effect of microencapsulation. However, Eyles fail to disclose any adjuvant other than CTB.

Furthermore, Eyles provide no teaching or motivation to one of ordinary skill in the art to make and/or use a polycationic carbohydrate comprising chitosan. Moreover, there is no motivation or suggestion to make and/or use a polycationic carbohydrate, wherein the polycationic carbohydrate comprises a water soluble alkylated chitosan composition, as claimed herein. As stated above, neither Eyles or Illum teach or suggest the claimed alkylated chitosan composition and fail to provide a *prima facie* obviousness rejection. Accordingly, Applicants

submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claim 3 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Kotze et al., (hereinafter "Kotze").

Applicants respectfully traverse. As explained above, Illum fail to teach or suggest a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition. In addition, Claim 3 depends indirectly from the composition of Claim 1. As discussed above, Applicants respectfully submit the compositions of the instant application are novel and non-obvious over the teachings of Illum. Furthermore, the deficiencies of Illum are not satisfied by Kotze for at least the following reasons.

Kotze utilize N-trimethyl chitosan (TMC) as an absorption enhancer. In particular, Kotze investigate the effect of TMC on the electrical resistance of intestinal epithelial cells. Kotze report TMC to be as an effective absorption enhancer as chitosan hydrochloride and chitosan glutamate (see page 1202, column 1, first full paragraph). Clearly, Kotze teach away from the preferred use of TMC as an adjuvant because TMC is only as effective as chitosan glutamate (see Illum). In contrast, the Applicants of the instant application disclose TMC has an adjuvant effect. In addition, the Applicants demonstrate that TMC exhibits an increased adjuvant effect when compared with chitosan hydrochloride, see Example 3 (page 18) and Figure 2 of the instant application.

Accordingly, Applicants respectfully submit Illum and Kotze fail to provide a *prima facie* obviousness rejection because neither Illum or Kotze teach or suggest the compositions or methods as instantly claimed. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claim 22 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) and Eyles (discussed above) in view of Kotze et al., (discussed above).

Applicants respectfully traverse. As explained above, Illum and Eyles fail to teach or suggest a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition. In addition, Claim 22 depends indirectly from the composition of Claim 1. As discussed above Applicants respectfully submit the compositions of the instant application are novel and non-obvious over the teachings of Illum and Eyles. Furthermore, the deficiencies of Illum and Eyles are not satisfied by Kotze for at least the following reasons.

The Examiner states it would be obvious to modify the composition as taught by Illum and Eyles to include cationic pluronic compounds that are surface modified with chitosan. Applicants assert that none of the prior art documents disclose the use of cationic pluronics. Furthermore, Applicants respectfully submit that neither Illum, Eyles or Kotze teach or suggest cationic pluronic particles coated with chitosan. In contrast, the Applicants disclose cationic pluronic particles can be used as an adjuvant in vaccine compositions (see page 11, lines 6-18). Furthermore, it is to the Applicants credit that pluronic compounds and chitosan can be used in combination as vaccine adjuvants and immunostimulants.

As stated above, Kotze utilize N-trimethyl chitosan (TMC) as an absorption enhancer and report that TMC is only as effective as chitosan glutamate (see Illum) or chitosan hydrochloride. In contrast, the Applicants demonstrate that TMC exhibits an increased adjuvant effect when compared with chitosan hydrochloride, see Example 3 (page 18) and Figure 2 of the instant application. Clearly, the teachings of Kotze would not motivate one of ordinary skill in the art to make and/or use the instant composition. Accordingly, Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Non-Final Office Action mailed October 1, 2004, the Examiner rejected Claim 23 under 35 U.S.C. §103(a), as being unpatentable over Illum (WO 97/20576) (discussed above) in view of Eyles (discussed above).

Applicants respectfully traverse. As explained above, Illum and Eyles fail to teach or suggest a polycationic carbohydrate or a pharmaceutically acceptable derivative thereof, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition. In addition, Illum and Eyles fail to teach or suggest a method for producing a pharmaceutical

composition wherein the method comprises encapsulating a biological active agent in the presence of a polycationic carbohydrate, wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan composition. Claim 23 depends indirectly from the composition of Claim 1, and for at least the reasons presented above, Applicants assert Claim 1 is novel and non-obvious over the prior art of record. Accordingly, Applicants respectfully submit Claim 23 is also novel and non-obvious over the teachings of Illum and Eyles. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

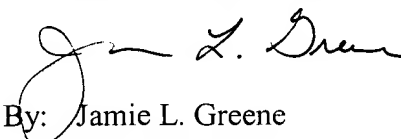
### CONCLUSION

Based upon the amendments and remarks provided above, Applicants believe that Claims 1-39 are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

A check for additional claims is submitted herewith. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,

  
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